Message

From: Kausch, Jeannine [Kausch.Jeannine@epa.gov]
Sent: 5/27/2016 12:46:16 PM
To: Wozniak, Chris [wozniak.chris@epa.gov]; Djurickovic, Milutin [Djurickovic.Milutin@epa.gov]; Kough, John [Kough.John@epa.gov]; Borges, Shannon [Borges.Shannon@epa.gov]
CC: Murasaki, Seiichi [Murasaki.Seiichi@epa.gov]; Carlisle, Sharon [Carlisle.Sharon@epa.gov]; Nesci, Kimberly [Nesci.Kimberly@epa.gov]
Subject: FW: Additional Data/Information Needed for 88877-EUP-E Application
Attachments: Univ. Ky-CA response to EPA issues of 09-29-15,10-06-15.docx

Flag: Follow up

FYI . . . Here's the response from the University of Kentucky that was received in response to some of the issues raised in Milutin and John's review of August 27, 2015. (The August 27, 2015, review is attached to the email that I just sent.) This response was evaluated in the October 14, 2015, review from John. (The October 14, 2015, review is attached to the email that I just sent.)

From: Robert Rose [mailto:rirose21@gmail.com]
Sent: Tuesday, October 06, 2015 3:26 PM
To: Kausch, Jeannine <Kausch.Jeannine@epa.gov>
Cc: Borges, Shannon <Borges.Shannon@epa.gov>; Carlisle, Sharon <Carlisle.Sharon@epa.gov>; Dobson, Stephen L <sdobson@uky.edu>; James Mains <jimmymains@gmail.com>; Corey Brelsfoard <clbrel2@gmail.com>
Subject: Re: Additional Data/Information Needed for 88877-EUP-E Application

Hi Jeannine:
The registrant response addressing EPA-OPP-BPPD product characterization and toxicology issues of 09/29/2015 concerning the 88877-EUP-E application is attached as a Word document by Drs. Stephen Dobson, James Mains, & Corey Brelsfoard.
I hope all requirements have now been satisfied and the EUP may be approved accordingly.
Best regards,
Bob
(301) 874-5593

On Tue, Sep 29, 2015 at 8:34 AM, Kausch, Jeannine <Kausch.Jeannine@epa.gov> wrote:

> Hi Bob,
>
> The product characterization and toxicology reviewer for your 88877-EUP-E application has brought up some issues that will have to be addressed to allow us to make a decision on this particular action. The issues are as follows:
>
> (1) Address the research results reported in Dodson et al. (2014), Glaser & Meola (2010), Hughes et al. (2014) and Hussain et al. (2013). Specifically, Dodson et al. (2014) reported wAlbB infected *Culex tarsalis* may increase West Nile Virus infection rates and reduce gene expression of the REL1 (antiviral Toll pathway). While it is clear more research is necessary, please address this finding and how it relates to *Aedes aegypti* wAlbB releases and the potential or probability of increased infection rates and reduced immune gene expression of West Nile Virus in wAlbB infected mosquitoes. Also, please discuss your opinion on if these findings are due to host type, *Wolbachia* strain type, or both. Include a discussion on how other environmental

factors such as temperature, as described by Hughes et al. (2014), may influence West Nile Virus infection rates, immune gene expression of antiviral pathways, and transmission potential. Reconcile the differences in the literature between Dodson et al. (2014), Hughes et al. (2014), Glaser & Meola (2010), and Hussain et al. (2013), which reported increased host resistance to West Nile Virus with *Wolbachia* presence in *Aedes aegypti* and *Culex quinquefasciatus*. The differences are most likely due to difference in strain and host uses. Unfortunately, no report was found by the EPA that specifically discusses *Aedes aegypti* wAlbB and West Nile Virus.

(2) Provide statistical analysis of your data for the inferential power of your claim that 1 female wAlbB strain is expected per 250,000 individuals released. According to Calvitti et al. (2015), the current sexing technology is such that 1% female contamination is expected during male releases. Discuss how and why your sexing technology is superior to this.

(3) Address the report by Calvitti et al. (2015) that fertile crosses between wAlbA low density males and ARwP females demonstrate that mosquitoes with differing *Wolbachia* strains may still be fertile, and how this finding impacts *Wolbachia* male release strategies. Discuss how the finding in this study that the risk of bidirectional CI failure should be evaluated by sampling wild type males prior to field releases. And, if pertinent, present data on sampling of male pre-releases.

References Cited:

Calvitti M, Marini F, Desiderio A, Puggioli A, Moretti R. 2015. *Wolbachia* density and cytoplasmic incompatibility in *Aedes albopictus*: Concerns with using artificial *Wolbachia* infection as a vector suppression tool. PloS one 10: e0121813. Available from *http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0121813*.

Dodson BL, Hughes GL, Paul O, Matacchiero AC, Kramer LD, Rasgon JL. 2014. *Wolbachia* enhances West Nile Virus (WNV) infection in the mosquito *Culex tarsalis*. PloS one 8: e2965. Available from *http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0002965*.

Glaser RL, Meola MA. 2010. The native *Wolbachia* endosymbionts of *Drosophila melanogaster* and *Culex quinquefasciatus* increase host resistance to West Nile Virus infection. PloS one 5: e11977. Available from *http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0011977*.

Hughes GL, Rivero A, Rasgon JL. 2014. *Wolbachia* can enhance *Plasmodium* infection in mosquitoes: Implications for malaria control? PloS one 9: e1004182. Available from *http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1004182*.

Hussain M, Lu G, Torres S, Edmonds JH, Kay BH, Khromykh AA, Asgari S. 2013. Effect of *Wolbachia* on replication of West Nile Virus in a mosquito cell line and adult mosquitoes. *Journal of Virology* 87: 851–858. Available from *http://jvi.asm.org/content/87/2/851.full*.

After reading through these issues and discussing them with the UK scientists, can you let me know when you think you would be able to provide a complete response? The current PRIA due date for this action is set to October 19, 2015, but this may need to be negotiated to allow you to respond and our reviewers an opportunity to evaluate your response. Also, if you have any technical questions about the issues raised above, I will likely need to bring one of our science reviewers into the conversation to clarify.

Thanks for your continuing cooperation and responsiveness regarding this application.

Regards,

Jeannine

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